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Physiologic Significance of Chronic Coronary Aneurysms in Patients With Kawasaki Disease

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Objectives. **The aim of this study was to determine whether persistent coronary aneurysms in patients with Kawasaki disease are associated with altered myocardial perfusion and function.**

Background. **Some patients with Kawasaki disease have died suddenly because of severe coronary artery stenosis; others have chronic coronary aneurysms.**

Methods. **Eleven patients with chronic coronary aneurysms were enrolled in the study. The size of the aneurysms and the degree of associated stenosis were determined by angiography in nine patients and by echocardiography in two. All patients underwent simultaneous function and myocardial perfusion assessment during symptom-limited exercise by echocardiography and technetium-99m sestamibi imaging, respectively.**

Results. **Of 33 vascular territories, 18 contained coronary aneurysms measuring 3.5 to 10 mm. Three aneurysms were associated with significant stenosis as detected by angiography. Of the 18 vascular territories, 13 were normal, and 5 manifested stress-induced perfusion defects; of the latter 5 areas, 4 had associated wall motion abnormalities. The three territories supplied by stenotic coronary arteries had both abnormal regional function and perfusion demonstrated during exercise.**

Conclusions. **Patients with chronic coronary aneurysms may have associated stenosis, as detected by angiography, with a subjacent myocardium that is subject to abnormal perfusion and function. However, the majority of coronary aneurysms are associated with normal regional coronary flow reserve, as assessed by myocardial perfusion imaging, and even giant coronary aneurysms may be associated with normal coronary flow reserve and preserved regional myocardial function during stress.**

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Kawasaki disease is an acute inflammatory febrile illness associated with culture-positive toxin-secreting staphylococci and streptococci (1) that can cause coronary artery dilation, aneurysms or stenoses. Before the introduction of intravenous gamma globulin therapy for Kawasaki disease, approximately 15% to 20% of affected children developed coronary artery abnormalities (2–4). If treatment with intravenous gamma globulin is initiated within 10 days of the onset of the illness, the frequency of these abnormalities is reduced to 4% by 7 weeks after the onset of the disease (5,6). Within the 1st 2 years of illness 30% to 50% of such aneurysms spontaneously regress (2,7). The remaining aneurysms become chronic and may become stenotic and obstructive over the years. The late mortality rate associated with coronary artery involvement is estimated to be 0.1% to 0.5% and is thought to be related to myocardial infarction secondary to coronary artery stenoses with impaired myocardial perfusion. However, the effect of chronic coronary artery aneurysms on myocardial and regional ventricular function in the majority of patients is not well understood. Therefore, the purpose of the study was to assess how coronary aneurysms with or without stenosis that occur in association with Kawasaki disease affect regional myocardial perfusion and regional ventricular function during exercise.

Methods

Patients. Eleven patients, seven male and four female, with chronic coronary artery aneurysms documented by echocardiography were enrolled in this study at a median age of 11 years (range 5.2 to 17.4). The median age at initial diagnosis of Kawasaki disease was 6 years (range 0.7 to 15.7) with a median interval of 3 years (range 1.2 to 14) from the onset of Kawasaki disease. Six of 11 patients received intravenous gamma globulin at the time of diagnosis; the condition of the other 5 patients was diagnosed before the introduction of gamma globulin therapy for Kawasaki disease. All patients met the clinical criteria for Kawasaki disease and all had abnormal coronary artery dimensions documented by echocardiography. Their median weight at the time of study was 40 kg (range 27.5 to 77.5). All patients were asymptomatic during routine daily

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activities and had a normal 12-lead electrocardiogram (ECG) at rest. Written informed consent to perform all studies was provided by the children's parents.

Cardiac catheterization. Nine of the 11 patients underwent routine right and left heart catheterization with selective coronary angiography to assess the diameter of normal, aneurysmal and stenotic coronary arteries. In two patients who refused catheterization, two-dimensional echocardiography was used to assess the proximal coronary arteries.

Stress echocardiography. Within 1 month of angiography, all patients underwent stress echocardiography with a protocol that required the patient to pedal at a rate of 60 rpm on a supine bicycle ergometer (KHL Inc.) tilted 30° to 45° in the left lateral decubitus position. Every 3 min the work load was increased (at increments adjusted for body surface area) until the 60-rpm pedaling rate could no longer be maintained. Long-axis, short-axis, apical four- and two-chamber views of the left ventricle were acquired at rest and during the last minute of each work load with the use of a Vingmed or Hewlett-Packard Sonos 1000 echocardiography machine. Images obtained at rest and at the patient's peak work load were compared side by side in cine loop mode by two experienced cardiologists using semiquantitative visual analysis. One patient (Case 7) had flattening of the T waves in the anterolateral leads during peak exercise.

Stress perfusion single-photon emission computed tomography. At peak exercise, approximately 0.314 mCi/kg of technetium-99m hexakis 2-methoxyisobutyl isonitrile (sestamibi) was injected and the stress activity was continued for at least 2 min after the injection to optimize myocardial uptake of the isotope during peak exercise. Imaging was then performed ~30 min after the injection. Single-photon emission computed tomographic (SPECT) imaging was performed on a Siemens Orbiter camera. Images were obtained in a 180° circular orbit beginning from the 45° right anterior oblique to the 45° left posterior oblique projection. For the acquisition, 64 projection images (20 s/projection) were acquired, and a 20% window centered on the 140-keV peak was employed. Images were stored on a 64 × 64, 16-bit matrix. The raw sestamibi data were reconstructed by using a Butterworth filter with a 0.55 cutoff and an order of 2.5.

Patients who demonstrated a stress-induced perfusion defect were brought back on a subsequent day for a rest sestamibi study, to characterize the stress perfusion defect as ischemia or infarct. Using technetium-99m sestamibi to obtain rest images, ~0.314 mCi/kg of sestamibi was injected and then flushed with 10 ml of saline solution. At ~10 min after injection, patients were given 8 oz (236.6 ml) of whole milk to increase hepatic clearance of the isotope. Technetium-99m sestamibi image acquisition began 1 h after the rest injection using the same acquisition protocol as described before. The raw sestamibi data were then reconstructed by using a Butterworth filter with a cutoff of 0.4 and an order of 3.5. The stress images were subsequently compared with the rest images to assess for defect reversibility suggesting myocardial ischemia. The images were read by using visual analysis to determine the presence (or absence), location and reversibility of stress perfusion defects by two experienced readers who had no knowledge of the clinical, angiographic and echocardiographic data.

Statistical analysis. A logistic regression model was used to evaluate the effect of aneurysm size on the probability of a perfusion defect. The method of generalized estimating equations (8) was used to take into account the correlation of multiple outcomes within a subject. Because of the small sample size, the intrasubject correlation was not estimated. A range from 0.25 to 0.75 was investigated and the resulting estimates were not sensitive to the chosen value of 0.5. In this analysis an aneurysm in the left main coronary artery was treated as two aneurysms of the same size in the left anterior descending and left circumflex coronary arteries, because they are branches of the left main coronary artery. Thus, the data set consisted of 18 observations in 11 subjects.

Results

The clinical and exercise data of the 11 patients as well as the results of the stress ECG, echocardiogram and the stress myocardial perfusion scan are shown in Table 1.

Angiography. Of the 33 vascular territories in the 11 patients, 18 territories (55%) had coronary aneurysms on coronary angiography. The diameters of the aneurysms on angiography (in nine patients) and on echocardiography (in two patients) ranged from 3.5 to 10 mm. Two patients (Cases 7 and 9) had a total of three aneurysms complicated by significant stenoses distal to the aneurysm. Patient 7 had a reduced ejection fraction of 40%; the other 10 patients had normal left ventricular function documented by angiography or echocardiography, or both.

Exercise stress test. The mean peak heart rate during exercise was 179 ± 13 beats/min (86 ± 8% of that predicted for age). All patients were asymptomatic during exercise except for Patient 7, who developed chest pain indicative of ischemia associated with flattening of the T waves in the anterolateral leads of the ECG.

Single-photon emission computed tomography. Of the 18 vascular territories with coronary aneurysms, 5 territories (28%) in four patients were associated with stress-induced perfusion defects; the remaining 13 territories had normal regional perfusion during exercise. The three vascular territories with aneurysms complicated by stenoses all had reversible stress-induced perfusion defects indicative of inducible ischemia. None of the vascular territories without aneurysms developed perfusion defects during exercise. The angiogram of Patient 7 (Fig. 1A) shows significant aneurysms in the left anterior descending and left circumflex coronary arteries complicated by severe stenosis. The SPECT image of the same patient (Fig. 1B) shows the presence of stress-induced perfusion defects corresponding to the areas supplied by the involved arteries, whereas the rest perfusion images were normal, consistent with inducible ischemia.

Table 1. Patient Data and Results of Angiography, Stress Perfusion Scan and Stress Echocardiography

Pt No.	Gender	Age (yr) At Onset of Disease	Age (yr) At Study	Interval (yr) From Onset of Disease to Study	Aneurysm Site* (size in mm)	SPECT	Stress ECG	Stress Echo	Peak HR (beats/min)
1	F	6	11	5	LAD (5.4)	Pos	Neg	NL	170
2	M	3	17	14	LMCA (5.3)	Neg	Neg	NL	181
					RCA (9.5)	Neg		NL	
3	M	0.67	8	7.33	LMCA (5.5)	Neg	Neg	NL	175
4	M	4	5.17	1.17	LAD (10)	Neg	Neg	NL	179
5	F	1.17	13.17	12	LAD (5.7)	Pos	Neg	Pos	166
6	M	12.67	14.92	2.25	LMCA (3.5)	Neg	Neg	NL	215
7	M	0.83	10.58	9.75	LMCA (8.5)	Pos	Neg	Pos	169
					RCA (4)	Pos		Pos	
8	M	6.25	8.25	2	RCA (9.1)	Neg	Neg	NL	171
9	F	9	11.58	2.58	LAD (9.9)	Pos	Neg	Pos	182
					RCA (7.7)	Neg		NL	
10	M	15.7	17.37	1.67	RCA (3.5)	Neg	Neg	NL	178
11	F	7	8.42	1.42	LAD (3.5)	Neg	Neg	NL	180

*The aneurysm site and size were determined by angiography in 9 of the 11 patients and by echocardiography in Patients 1 and 2. ECG = electrocardiography; Echo = echocardiography; F = female; HR = heart rate; LAD = left anterior descending coronary artery; LMCA = left main coronary artery; M = male; Neg = negative; NL = normal; Pos = positive; Pt = patient; RCA = right coronary artery; SPECT = single-photon emission computed tomography.

Stress echocardiography. Of the 11 patients studied, only 3 (Cases 5, 7 and 9) had exercise-induced echocardiographic wall motion abnormalities. These abnormalities occurred in regions corresponding to vascular territories supplied by the coronary aneurysms. Wall motion was normal at rest in these territories, suggesting that the wall motion abnormalities were due to stress-induced ischemia.

Of the five vascular territories with perfusion defects, four in three patients showed wall motion abnormalities on stress echocardiography. Three of those areas were in the two patients (Cases 7 and 9) who had aneurysms complicated by stenoses (Fig. 1). Thus, although the majority of coronary aneurysms were not associated with stenosis, the presence of perfusion or functional abnormalities during stress accurately identifies patients with aneurysms complicated by stenoses.

Patient 7 developed chest pain during exercise: because the perfusion and functional abnormalities were reversible at rest, the findings suggest extensive territories of inducible myocardial ischemia. This patient subsequently underwent revascularization surgery. Results of a repeat stress perfusion scan performed 2 months postoperatively utilizing the same protocols were entirely normal. The reversal of these stress-induced perfusion abnormalities after coronary artery bypass grafting supports the concept that the scan abnormalities were indeed due to reversible myocardial ischemia.

With the use of generalized estimating equations (8) and a logistic regression model, it was estimated that a 1-mm increase in aneurysm size increases the odds of a perfusion defect by a factor of 1.14 (95% confidence interval: 0.86–1.52, $p = 0.36$). These data do not reject the null hypothesis of no association between aneurysm size and perfusion defect at the 0.05 level, but this observation does not mean that they support the null hypothesis. A theoretical calculation showed that the power of this study to detect an odds ratio of 4 is 85%, but to detect an odds ratio of 2 it is 63% (see Appendix).

Thus, this study with its limited sample size suggests the absence of a strong association, but does not have enough power against a weak association. An example of this lack of association is evident in Patient 5 (Fig. 2), who had a small caliber aneurysm in the left anterior descending coronary artery and a stress perfusion defect in the area corresponding to the aneurysm. In contrast, Patient 4 (Fig. 3) had a giant coronary aneurysm associated with a normal stress perfusion scan.

Discussion

In patients with Kawasaki disease, 30% to 50% of coronary aneurysms regress spontaneously within the first year of the illness (2,7). How aneurysms that do not regress affect coronary flow reserve has not been well studied. Hamaoka et al. (9) studied the effect of Kawasaki disease on coronary flow reserve in patients without aneurysms or stenosis by measuring coronary sinus blood flow at rest and during atrial pacing. Compared with findings in normal children, the coronary reserve flow in these patients was reduced during pacing, suggesting that such patients have reduced dilating capacity of the small coronary arteries that are not seen by coronary angiography. Fukazawa et al. (10) found significant discordance between thallium-201 SPECT imaging of myocardial perfusion during stress and coronary angiograms. In particular, some patients without angiographic evidence of coronary abnormalities had abnormal scan, again suggesting involvement of small coronary arteries (9,10).

In this study, we demonstrated that three aneurysms in two patients were associated with significant stenoses not evident

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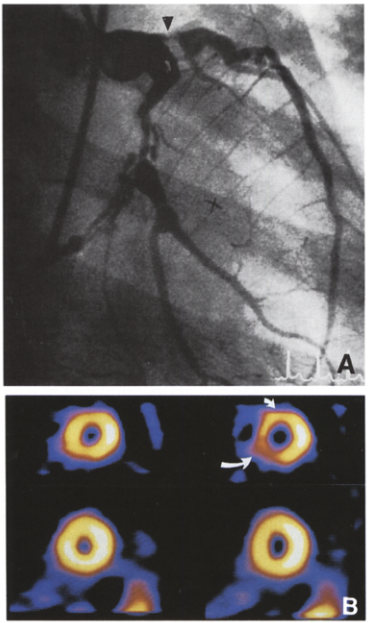

Figure 1. Patient 7. **A,** Coronary angiogram, right anterior oblique projection. The **arrowhead** indicates the site of severe stenosis. **B,** Stress (**upper images**) and rest (**lower images**) single-photon computed tomographic (SPECT) sestamibi images in the short-axis view (*similar to an echocardiographic short-axis view*). The decreased uptake (**arrows**) reveals the presence of a stress perfusion defect in the septal and anterior walls. The rest images are normal.

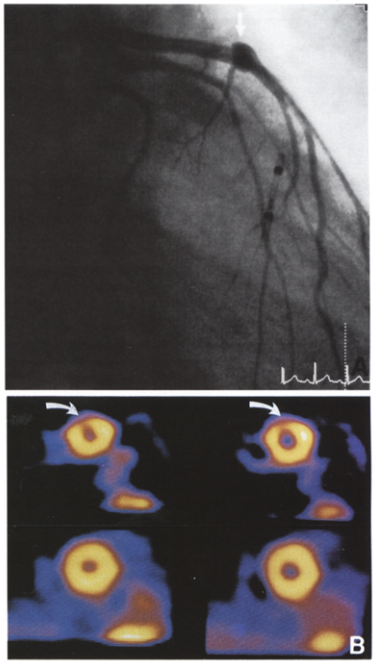

Figure 2. Patient 5. **A,** Coronary angiogram, right anterior oblique projection. A small-caliber aneurysm (**arrow**) is evident in the left anterior descending coronary artery. **B,** Stress (**upper images**) and rest (**lower images**) single-photon computed tomographic (SPECT) sestamibi images in the short-axis view. A stress-induced perfusion defect in the anterior wall (**arrows**) is evident. The rest images are normal.

by echocardiography. However, the majority of aneurysms, even those up to 10 mm in diameter, were not associated with ECG, perfusion or functional abnormalities during stress. Only 28% of the aneurysms were associated with an abnormal stress perfusion scan and only 22% with inducible wall motion abnormalities. Although the sample size is small, the data did not reject the null hypothesis of no association between aneurysm size and the presence of perfusion defect; it also did not support it. However, the presence of stress-induced perfusion or functional abnormalities indicated that there was a high likelihood of a stenosis complicating the aneurysm; all patients with stenoses were identified by analysis of both stress perfusion defects and abnormal wall motion.

Pharmacologic stress thallium-201 imaging using the coronary arteriolar vasodilator dipyridamole offers an alternative method to exercise stress, especially in young pediatric patients unable to exercise to an adequate end point. Kondo et al. (11) demonstrated the safety and efficacy of dipyridamole stress thallium-201 myocardial perfusion SPECT imaging in 23 normal children and 49 patients with Kawasaki disease and found this method of evaluating coronary abnormalities to be accurate for detecting coronary stenosis. Takahashi et al. (12), using technetium-99m sestamibi and thallium-201 in 13 patients with Kawasaki disease, found that stress perfusion scans were sensitive but not specific for detecting coronary stenosis,

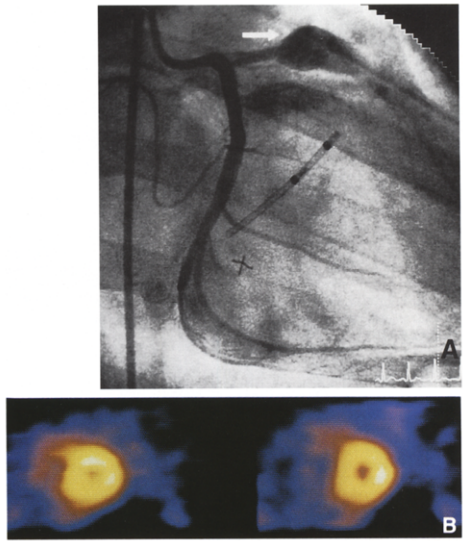

Figure 3. Patient 4. **A,** Coronary angiogram in the right anterior oblique projection. A giant aneurysm **(arrow)** is evident in the left anterior descending coronary artery. **B,** Stress single-photon computed tomographic (SPECT) sestamibi images in the short-axis view. Regional flow reserve is normal during stress.

because six of eight patients without coronary angiographic obstruction had abnormal scan findings. In contrast, the present data demonstrate that the majority of aneurysms not complicated by stenosis are associated with normal coronary flow reserve during stress.

In the present study, technetium-99m sestamibi was used as the myocardial perfusion tracer. The technetium label is associated with more favorable imaging characteristics than those of thallium-201, and its lack of "redistribution" (change in regional activity over time) allows imaging up to several hours after injection, with the resulting images reflecting myocardial blood flow at the time of injection (13).

Currently, patients at our institution with chronic coronary aneurysms undergo yearly evaluation with stress echocardiography and stress perfusion scans. Should one of these tests yield abnormal findings, then further evaluation with coronary angiography may be necessary because previous studies (14) have shown that a subset of uncomplicated coronary aneurysms eventually become complicated by obstructive stenosis. The current data suggest that screening for this occurrence with serial stress myocardial perfusion imaging or stress echocardiography over time may detect this phenomenon.

Conclusions. Patients with chronic coronary aneurysms may have associated coronary stenosis detected by angiography. Our study failed to reject the hypothesis of no association between aneurysm size and perfusion defects. Because of the small sample size our data suggest only the absence of a strong association. Patients with stenoses may be accurately identified by using stress imaging of myocardial perfusion or regional ventricular function. Most patients with aneurysms not complicated by stenosis have normal regional stress myocardial function and perfusion, although a minority with chronic coronary aneurysms without stenosis have abnormal stress perfusion scan findings.

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Appendix

A theoretic power calculation was performed as follows. Let p denote the probability of a positive SPECT, and let z denote the aneurysm size in mm (or the mean size in subjects with more than one aneurysm). This defines a design matrix with 11 rows and 2 columns (intercept and z). Suppose that a logistic model holds:

$$\text{logit } p = \log [p/(1-p)] = B_0 + B_1 z.$$

The variable B_1 is the log odds ratio associated with a 1-mm increase in aneurysm size. The intercept B_0 is chosen such that at the mean aneurysm size (6.25 mm), $p = 5/14$, which is the observed overall proportion. At the null hypothesis $B_1 = 0$, the asymptotic standard error (SE) of the estimator of B_1 is 0.283. So a large sample test, with type -1 error 0.05, rejects the null hypothesis if the estimate of B_1 is $>1.96 \times 0.283$ in absolute value. For alternative values of B_1 the asymptotic standard error is computed, and the normal approximation is used to compute power. The results are summarized in the following table:

B_1	SE	Power
log 1	0.238	0.05
log 2	0.411	0.63
log 4	0.830	0.85
log 8	1.480	0.89

These calculations suggest that there is reasonably good power in detecting an odds ratio in the range of 4 to ≥8 per 1-mm increase in aneurysm size.

References

1. Leung DYM, Meissner HC, Fulton DR, Murray DL, Kotzin BL, Schlievert PM. Toxic shock syndrome toxin-secreting Staphylococcus aureus in Kawasaki syndrome. Lancet 1993;342:1385–8.
2. Kato H, Ichinose E, Yoshioka F, et al. Fate of coronary aneurysm in Kawasaki disease: serial coronary angiography and long-term follow-up study. Am J Cardiol 1982;49:1758–66.
3. Suzuki A, Kamiya T, Kuwahara N, et al. Coronary arterial lesions of Kawasaki disease: cardiac catheterization findings of 1100 cases. Pediatr Cardiol 1986;7:3–9.
4. Kato H, Ichinose E, Kawasaki T. Myocardial infarction in Kawasaki disease: clinical analyses in 195 cases. J Pediatr 1986;108:923–7.
5. Newburger JW, Takahashi M, Burns JC, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. N Engl J Med 1986;315: 341–7.
6. Newburger JW, Takahashi M, Beiser AS, et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. N Engl J Med 1991;324:1633–9.
7. Pahl E, Ettedgui J, Neches WH, Park SC. The value of angiography in the follow-up of coronary involvement in mucocutaneous lymph node syndrome (Kawasaki disease). Am Coll Cardiol 1989;14:1318–25.
8. Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika 1986;73:13–22.
9. Hamaoka K, Onouchi Z, Ohmochi Y. Coronary flow reserve in children with Kawasaki disease without angiographic evidence of coronary stenosis. Am J Cardiol 1992;69:691–2.
10. Fukazawa M, Fukushige J, Takeuchi T, et al. Discordance between thallium-201 scintigraphy and coronary angiography in patients with Kawasaki disease: myocardial ischemia with normal coronary angiograms. Pediatr Cardiol 1993;14:67–74.
11. Kondo C, Hiroe M, Nakanishi T, Takao A. Detection of coronary artery stenosis in children with Kawasaki disease. Usefulness of pharmacologic stress ^{201}Tl myocardial tomography. Circulation 1989;80:615–24.
12. Takahashi M, Miller JH, Mason W. Myocardial perfusion abnormalities in chronic Kawasaki syndrome: lack of correlation with angiographic coronary obstruction [abstract]. J Am Coll Cardiol 1993;21 Suppl 2:474A.
13. Wackers FJT, Berman DS, Maddahi J, et al. Technetium-99m hexakis 2-methoxyisobutyl isonitrile: human biodistribution, dosimetry, safety, and preliminary comparison to thallium-201 for myocardial perfusion imaging. J Nucl Med 1989;30:301–11.
14. Onouchi Z, Hamaoka K, Kamiya Y, et al. Transformation of coronary artery aneurysm to obstructive lesion and the role of collateral vessels in myocardial perfusion in patients with Kawasaki disease. J Am Coll Cardiol 1993;21:158–62.